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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/785,632	02/16/2001	Jin-Soo Kim	12279-002001	3563
26161	7590	01/17/2006	EXAMINER	
FISH & RICHARDSON PC P.O. BOX 1022 MINNEAPOLIS, MN 55440-1022			DUNSTON, JENNIFER ANN	
			ART UNIT	PAPER NUMBER
			1636	

DATE MAILED: 01/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	Application No. 09/785,632	Applicant(s) KIM ET AL.	
	Examiner Jennifer Dunston	Art Unit 1636	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 20 December 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.
b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on 20 December 2005. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
(a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
(b) ☐ They raise the issue of new matter (see NOTE below);
(c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
(d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).

5. ☐ Applicant's reply has overcome the following rejection(s): _____.

6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

7. ☐ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: _____.

Claim(s) objected to: _____.

Claim(s) rejected: 1-23, 32, 33, 86, 88-93 and 95-98.

Claim(s) withdrawn from consideration: 24-31, 34, 35, 87, 94, 99, 107, 112 and 117-119.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).

9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).

10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see continuation sheet.

12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____

13. ☐ Other: _____.

CONTINUATION SHEET

Applicant's amendment of the claims to delete the phrase "non-naturally occurring" in the response filed 4/4/2005 necessitated the rejections presented on pages 3-13 of the prior Office action. Barbas et al teach the mutagenesis of naturally occurring zinc finger proteins. Mutations naturally occur in cells as they divide. Thus, the genus of naturally occurring proteins is extremely large and not completely defined. One cannot say definitively if any one protein is non-naturally occurring because all of the natural proteins are not known. Therefore, the amendment of the claim to recite the limitation "non-naturally occurring protein" would obviate the art rejections of record. However, rejections under 35 U.S.C. 112, 1st paragraph would be made for the reasons presented on pages 5-8 of the Office action mailed 6/2/2004. For these reasons, and the reasons made of record in the previous office actions, the finality of the Office action mailed 6/20/2005 is maintained.

Applicant's arguments filed 12/20/2005 have been fully considered but they are not persuasive.

The response asserts that the Office action does not establish a *prima facie* case of obviousness because there is no reasonable expectation of success or motivation to combine the Barbas and Cheng references. The response asserts that there is no reason to believe that the method taught in Cheng et al is suited for evaluating different zinc finger domains because Cheng et al fail to show that any zinc finger domain other than the original Sp1 zinc fingers was functional in the *in vivo* method.

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In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Barbas teach that the Zif268 zinc finger sequences can be mutated so that the proteins recognize a nucleotide sequence other than the sequence originally recognized by the Zif268 protein. Further, the sequence modifications taught by Barbas et al maintain the zinc finger consensus sequences (e.g. column 45, lines 18-61). As stated in the prior Office action, "It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the piecewise mutagenesis of three zinc fingers in a polypeptide to each bind to a corresponding altered part of the nucleotide sequence to which the polypeptide binds, testing the polypeptides that each contain one of the mutagenized zinc fingers for binding to the target nucleotide sequence by the use of phagemid display/affinity, followed by constructing a nucleic acid that encodes all three mutagenized fingers, taught by Barbas, by substituting the phagemid display/affinity selection with the in vivo expression method taught by Cheng et al because Cheng et al teach that it is within the skill of the art to use the in vivo expression method to identify peptide-DNA binding interactions, and Cheng et al specifically teach the use of this method to identify a peptide from a randomized library which binds to an altered target sequence in a polypeptide that also comprises two unaltered zinc fingers that bind the rest of the DNA sequence which is also not altered." One would expect that at least some zinc finger proteins

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containing a mutation in one of three zinc fingers that are capable of binding to a target sequence by phagemid display/affinity selection, as taught by Barbas et al, would be capable of binding to a target sequence *in vivo* using the method of Cheng et al where the binding site corresponding to the mutated zinc finger is provided in the assay. Cheng et al teach that the three zinc fingers of Sp1 are capable of functioning in the assay when the appropriate binding site is provided in the assay. Thus, one would necessarily expect at least some of the nucleic acids that encode proteins comprising three zinc fingers, as taught by Barbas et al, would function in the method of Cheng et al. As stated in the prior Office action (pages 9-10), one would have been motivated to combine the teachings of the two references for the expected benefit of identifying the altered zinc finger peptides which bind to altered target sites in a biologically significant fashion that thus result in making a nucleic acid that encodes a polypeptide that has a biologically significant peptide-DNA binding interaction with the altered nucleic acid sequence, as taught by Cheng et al. Thus, Cheng et al provide a motivation to combine the two references.

The response asserts that the method of Cheng et al identifies domains that differ from zinc finger domains and thus teaches away from the combination of references. This is not found persuasive because Barbas et al define a plurality of nucleic acids encoding proteins of three zinc fingers, wherein one zinc finger has been mutagenized but still retains the ability to form a zinc finger.

The response asserts that Cheng et al never verify whether its identified peptides increased transcription *in vivo* by contacting DNA. Further, the response suggests that the peptides might operate by other modes such as stabilizing the reporter protein. This is not found persuasive because the claimed method recites that the step of measuring the expression of a

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reporter gene will identify a hybrid nucleic acid encoding a test zinc finger domain that recognizes the target site. This limitation is met by the combined teachings of Barbas et al and Cheng et al. Cheng et al teach that a sequence that is capable of being bound only by two zinc fingers is insufficient for gene expression, whereas a sequence capable of being bound by three zinc fingers can support gene expression. For the gene expression to occur in vivo all three zinc fingers are required to bind to the nucleic acid sequences (i.e. the "recruitment site" and "target site" of the instant claims). Barbas et al teach proteins of three zinc fingers.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

For these reasons, and the reasons made of record in the previous office actions, the rejections of record are maintained.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached at 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Jennifer Dunston
Examiner
Art Unit 1636

jad

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PATENT EXAMINER

